1115 POSTER*

Phase I and pharmacokinetic study of CHOP/MGBG (CM) in patients with Non-Hodgkin's-Lymphoma

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Purpose: To determine the Maximum Tolerated Dose (MTD), Dose Limiting Toxicity (DLT) and pharmacokinetics of M when combined with C.

Methods: Phase I study with increasing doses of M (400–700 mg/m^2) q 21 days in patients (pts) with intermediate or high-grade Non Hodgkin's-Lymphoma.

Results: 28 pts are evaluable for toxicity (t) (CTC), 22 for response (r) (WHO) and response duration (rd):

Dose MGBG	No of pts t/r	WBC 3/4	ANC 3/4	CR	PR	rd/range (months)
400 mg/m^2	13/12	5/6	0/11	5	5	17+/3+–26+
500 mg/m^2	6/4	2/4	0/6	3	1	12+/9+–14+
600 mg/m^2	6/4	2/4	0/6	2	2	8.5+/6+–9+
700 mg/m^2	3/2	1/1	1/2	0	2	4+/1+–7+

Thrombocytopenia grade 3 occurred in 1 pt at 400 mg/m^2, non-hematologic t grade 3/4 consisted of infection grade 3 in 1 pt at 400 mg/m^2. 6 pts were evaluated with 18 FDG-positron emission tomography at days 0, 8 and 42. Median decrease of 18 FDG-uptake on day 8 was 75% (range 56–86%) and on day 42 85.7% (range 85.7–88.5). Pharmacokinetic parameters at 400 mg/m^2 were: $t_{1/2\alpha}$ 0.19 h, $t_{1/2\beta}$ 2.07 h, $t_{1/2\gamma}$ 135.91 h, AUC 88.76 μgxh/mL, CL 5.19 L/h/m^2. Accrual is ongoing to determine the MTD of CM.

Conclusion: M can be combined with C at full doses. CM is a safe and active regimen warranting further evaluation.

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A phase I study of MTA (multi-targeted antifolate, LY231514) plus cisplatin (CIS) in patients with advanced solid tumours

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Purpose: MTA (LY231514) is a novel multi-targeted antifolate that inhibits thymidylate synthase and other folate-dependent enzymes. It has shown antitumour activity in preclinical models and early clinical trials. The study objectives were to determine the maximum tolerated dose (MTD) and dose-limiting toxicity of MTA (as a 10-min infusion) followed by CIS (1-hr infusion), every 21 days.

Methods: Pts with advanced/metastatic solid tumours (WHO PS ≤ 2) for whom no better treatment was available were eligible. Five dose levels were evaluated.

Dose level (mg/m^2)		Number of:		CTC Grade III/IV toxicity (# pts)		
MTA	CIS	pts	courses	neutropenia	leucopenia	↓platelets
1) 300	60	6	23	0/1	2/0	0/1
2) 300	75	6	16	5/1	4/0	0/0
3) 400	75	6	13	2/1	1/0	0/0
4) 500	75	3	5	0/5	0/0	0/2
5) 600	75	5	ongoing	0/0	0/0	0/1

Results: To date, 26 pts have been enrolled (4 F/22 M; median age 57 years, range 43–73). One pt developed Grade III mucositis. No major liver or renal toxicity was observed. The MTD has not yet been reached. Partial responses were noted at Level 1 (1 NSCLC; 1 colorectal), Level 2 (1 gastric) and Level 3 (1 unknown primary).

Conclusions: MTA and CIS can be given together at full doses. This combination shows promising activity in patients with advanced/metastatic solid tumours.

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Phase I study of Interleukin-4 (rHuIL-4) combined with chemotherapy in gastrointestinal (GI) malignancies

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IL-4 is a pleotropic cytokine which has shown tumor growth inhibition and synergy with chemotherapy in animal models. The safety of rHuIL-4, given in combination with 5-FU/Leucovorin (FA) chemotherapy, was evaluated in 15 patients (pts) with advanced GI malignancies. Cohorts of 3–6 pts received rHuIL-4 by SC injection, TIW for 4 weeks at dose levels of 0.5, 2.4 or 8 μg/kg, as well as 5-FU (425 mg/m^2) plus FA (25 mg/m^2) by daily IV infusion for 5 days in Wk1. In addition to standard safety evaluations, measurement of the kinetic (PK) profile of 5-FU was performed on D1 and D4. Age range was 26–74; 9 were male and 14 had colorectal tumors. Six pts had prior radiation; 10 had prior FU-based chemotherapy. The most frequently reported adverse experiences in the study were fatigue, nausea and fever (67–87%), which are expected from the known safety profiles of FU, FA or rHuIL-4. Grade 4 toxicities included neutropenia, headache, mucositis and vomiting (13–20%). No new toxicities were reported that were related to the combination of agents. DLT was seen in ≤2 pts in each cohort and an MTD for rHuIL-4 was not reached. PK analysis showed that concommitant administration of rising multiple doses of rHuIL-4 did not appear to effect the kinetics of 5-FU. Based on overall tolerability, a dose of 4.0 μg/kg rHuIL-4 was selected for further evaluation. Additional chemotherapy combinations will also be explored.

1118 POSTER

Absolute bioavailability and pharmacokinetics (PK) of oral vinorelbine (VRL) in patients (pts) with solid tumors

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The aim of this study was to compare body exposure and acute side effects of VRL administered either as an IV infusion (25 mg/m^2) or as capsules (80 mg/m^2), a new formulation. This was an open randomized Phase I-PK with cross-over design (one-week wash-out period). 25 and 31 pts out of 32 included are evaluable for PK and safety analysis respectively. Safety results: hematological toxicity: no significant difference between oral and IV VRL (G3–4 neutropenia: PO 27% – IV 10%). Nausea, vomiting: significant difference is observed when all grades are pooled (PO > IV) but grades 3–4 are rare and not different (G3 nausea: PO 3.3.% – IV 0%; G3–4 vomiting: PO 6.6% – IV 6.7%). Assuming dose-proportionality in both routes, bioavailability of the oral form is 43% ± 14. Higher blood AUCs are observed after oral administration as compared to IV ($p < 0.05$). Moreover, no increase in inter-individual variability is demonstrated for oral route compared to IV.

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Phase I clinical study of ecteinascidin-743 (ET-743) as a 24 hours continuous intravenous infusion (CI) in patients (pts) with solid tumors (st): A progress report

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ET-743 is a tetrahydroisoquinolone alkaloid from the tunicate *Ecteinascidia turbinata*, potently active in a variety of *in vivo* human xenograft models with long lasting complete remissions in melanoma, non small cell lung, breast and ovarian carcinoma. This activity may result from its unique mechanism of action as a DNA minor groove binding agent (guanine N2-specific sequence selectivity). Target organs in preclinical toxicity were bone marrow and liver. Pts with histological diagnosis of advanced stage ST, ECOG ≤ 2 and normal bone marrow, liver, renal function receive ET-743 iv 24 h CI every 21 days. As of 11/2/97, 11 pts were entered. Median age = 54 y (28–67) women/men = 7/2, median ECOG = 1 (0–2). Tumor types included breast (1), bladder (1), larynx (1), ovary (2), rectum (1), renal (3), gastric (1), and ACUP (1), all refractory to standard chemotherapy. Pharmacokinetics are performed on day 1 and day 2, and NCI-CTC grading criteria are applied for toxicity.